REMARKS

The present application is directed to methods of cloning genes using replication-deficient baculovirus vectors. Prior to this Amendment and Response, Claims 27-34 and 43-50 were pending. In the present Amendment and Response, applicants cancel Claims 43-50 and amend Claims 27 and 29. The amendments do not introduce any new matter. Upon entry of the present amendment, Claims 27-34 will be pending.

Applicants thank the Examiner for extending the courtesy of a telephone interview with their attorney on June 18, 2004.

Claim Amendments

Applicants amend Claim 27 to recite a "naked replication-deficient vector capable of being maintained in an intermediate host, wherein the intermediate host is a yeast cell or a bacterial cell." Support for the amendment is found throughout the specification. The baculovirus vector is required to be naked to use the transfection treatment as taught, for example, on p. 6, third paragraph. The specification teaches on p. 15 preparation of the baculovirus DNA from yeast and packaging it into the particles used to transfect the cells. The specification also teaches on p. 33 the use of viral DNA to transfect cells. The term "transfection" (infection of a cell with isolated viral nucleic acid followed by production of the complete virus in the cell, or the incorporation of exogenous DNA into a cell), and not "infection" (establishment of an infective agent, such as a virus) is consistently used throughout the specification, thereby demonstrating that it is naked viral DNA and not viral particles that is used in the applicants' claimed method.

The specification teaches the use of yeast or bacteria as an intermediate host, for example, on p. 7, third full paragraph.

Drawings

The Examiner objects to Figures 3B, 5 last panel, and 7 under 37 CFR 1.83(a) asserting the drawings fail to show any details as described in the specification. As recommended by the Examiner during the telephone interview on June 18, 2004, applicants hereby re-submit Figures 3B, 5 last panel, and 7.

Claim Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintains rejection of Claims 31-34 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

Claims 31-34 recite *lef 1-12, dnapol, pl43, p35, ie-1-2, p47, ORF 1629* and *pp 31* genes and functional fragments and mutations thereof. As stated by the Examiner, the written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Replying to the arguments provided by the applicants in the Response filed January 5, 2004, the Examiner asserted that "the single species specifically disclosed is not representative of the genus" and that "[n]either the prior art nor the specification teaches a correlation between structure and function." Applicants respectfully disagree.

Applicants respectfully assert that the specification discloses all of the recited species (*lef 1-12, dnapol, pl43, p35, ie-1-2, p47, ORF 1629* and *pp 31* genes) on page 6, central paragraph, along with a functional characteristic "necessary for replication."

At the time of filing of the present application, the structure of the claimed genes was known, as evidenced by the publications referenced on page 6, central paragraph. Therefore, the specification reasonably conveys to one of ordinary skill in the art relevant identifying characteristics of the claimed species. Based on the disclosure, one of ordinary skill in the art would know that the applicants had possession of a claimed method of cloning a gene using a replication-deficient baculovirus vector.

The Examiner asserts that applicants only disclose *lef-2* but do not disclose functional fragments or mutations thereof and that "any functional fragment or mutation must be empirically determined." Applicants respectfully disagree. Baculovirus is well-characterized. Production of functional fragments or mutations of genes, including baculovirus genes, is a matter of routine experimentation and was well established at the time of filing of the present application (see, for example, the following references cited in the Information Disclosure Statement: Kool *et al.* (1995) "Replication of Baculovirus DNA", Lu *et al.* (1995) "The role of eighteen baculovirus late expression factor genes in transcription and DNA replications", and Lu *et al.* (1997) "Baculovirus DNA replication"). Therefore, empirical determination by the applicants of all functional fragments or mutations is not necessary to convey to one of ordinary skill in the art that the applicants had possession of the claimed method of cloning a gene using a replication-deficient baculovirus vector.

It is the applicants position that the application, as filed, conveys to one of ordinary skill in the art that the functional genes, a representative number of which is disclosed in the specification, and their deletions and mutations fall within the claimed method of cloning a gene using a replication-deficient baculovirus vector.

In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claims 31-34 for reasons of insufficient written description under 35 U.S.C. §112, first paragraph.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner maintains the rejections of Claims 27 and 29 under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner asserts that the term "causing" recited in Claim 27 is unclear because "it is unclear what steps are required to be causative of the recombination." Applicants have amended Claim 27 to replace the term "causing" with the term "permitting." Support for the amendment is found, for example, on page 30, first paragraph, of the specification. The recombination event is spontaneous and is permitted by transfection of the two vectors into the insect cells. Applicants respectfully assert that the term "permitting" renders step iii of Claim 27 clear and renders Claim 27 definite.

The Examiner asserts that the expression "a gene necessary for restoring the functional gene" recited in Claim 29 is unclear because it does not differentiate between a functional gene required for viral replication and a gene that enzymatically restores the functional gene to its replication competent status. Applicants have amended the claim to recite expression of "a functional gene." Support for the amendment is found throughout the application, for example, in Claim 29 as originally filed. Applicants respectfully assert that the amendment renders Claim 29 definite.

Applicants respectfully assert that the amendments overcome the rejection of Claims 27 and 29 under 35 U.S.C. § 112, second paragraph and request withdrawal of the rejection.

Claim Rejections under 35 U.S.C. §103(a)

Clark in view of Patel

The Examiner maintains the rejection Claims 27-34 and 43-50 under 35 U.S.C. §103(a) as obvious over Clark *et al.* (hereinafter Clark), in view of Patel *et al.* (hereinafter Patel). Applicants cancelled Claims 43-50, thereby rendering their rejection moot. Applicants respectfully traverse the rejection of Claims 27-34.

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of Clark with the teachings of Patel to achieve economy of time and reduce costs, and that the modification would result in the applicants' invention as claimed with a reasonable expectation of success. Applicants disagree.

Clark teaches a recombinant baculovirus expression system that uses replication enablement as a selectable marker to screen for recombination events. Applicants respectfully assert that that the modification of the replication-deficient baculovirus vectors taught in Clark with the yeast or bacterial origin of replication would not result in the applicants' claimed invention.

In addition to using replication enablement as a selectable marker, the system taught in Clark requires the use of an apoptosis-deficient host-cell, *T.ni*, because the system relies on a modified baculovirus lacking an apoptosis-preventing gene. Using a host-cell line other than *T.ni* would result in cell death. The Clark system possesses a number of disadvantages, for example, it creates a heterogeneous virus population, rendering the stock of virus unusable for repeat experimentation. In contrast, applicants' system does not require using an apoptosis-deficient host cell line and does not create a heterogeneous virus population, and is non-obvious over the teachings of Clark for at least these reasons.

Furthermore, despite their replication deficiency, the vectors taught in Clark replicate at low levels in normal insect cells, resulting in contamination of the recombinant viral particles with the parent baculovirus. In contrast, applicants' claimed invention attains very high efficiency of recombination as compared to the Clark system and eliminates the need for time-consuming steps to separate recombinant virus from non-recombinant virus. Applicants respectfully assert that Clark fails to teach, suggest, or provide motivation to derive applicants' invention as claimed and fails to render applicants' claimed invention obvious.

The Examiner asserts that one of ordinary skill in the art would have been motivated to undertake the modification for the sake of reducing time consumption

and cost due to the lack of need for rounds of plaque purification. Applicants disagree. Clark fails to provide motivation to modify baculovirus vectors disclosed therein to enable their propagation in yeast or bacterial cells. Patel fails to teach, suggest, or provide motivation to derive applicants' invention as claimed, and fails to provide motivation to modify its teachings as suggested by the Examiner. Patel teaches generation of an infectious virus in yeast cells. In contrast, applicants' invention uses the yeast cell to maintain the replication-deficient baculovirus vector, which was generated in the insect cells. Patel fails to teach, suggest, or provide motivation to use insect cells to generate the recombinant virus in the insect systems. In fact, Patel teaches away from using insect systems for recombinant virus generation, asserting, that it is the yeast system that allows the rapid generation of the recombinant virus without any background parental virus (see, for example, on page 97, right-hand column, paragraph 3, and at the top of page 103, right-hand column).

In view of the foregoing, applicants respectfully assert that that one of ordinary skill in the art would not be motivated to combine the teachings of Clark and Patel to derive the applicants' invention as claimed with a reasonable expectation of success. Furthermore, modification of the teachings of Clark, as suggested by the Examiner, would fail to derive the applicants' invention, as claimed, and would fail to result in a method possessing the advantages of the applicants' invention. Applicants respectfully assert that Clark and Patel, separately or in combination, fail to render applicants' invention obvious. Applicants request withdrawal of the rejection under 35 U.S.C. §103(a) over Clark in view of Patel.

Kitts in view of Patel

The Examiner maintains the rejection of Claims 27-34 and 43-50 under 35 U.S.C. §103(a) as obvious over Kitts *et al.* (hereinafter Kitts) in view of Patel. Applicants cancelled Claims 43-50, thereby rendering their rejection moot. Applicants respectfully traverse the rejection of Claims 27-34.

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of Kitts with the teachings of Patel to achieve economy of time and reduce costs, and that the modification would result in applicants' invention as claimed with a reasonable expectation of success. Applicants disagree.

Kitts teaches a method of producing a recombinant baculovirus vector in insect cells that uses linearized baculovirus DNA in combination with standard transfer vectors, which results in the production of only 30-40% of recombinant viruses in the first round of plaque purification. In the Kitts method, some viral DNA always remains intact as an infectious circular molecule. Accordingly, contaminating parental virus is always present. Additionally, the use of linearized DNA in the Kitts method results in low yield of progeny virus. In contrast, applicants' claimed method uses a circular viral DNA and produces high yields of the progeny virus, with substantially 100% plaques containing recombinant viruses. Furthermore, Kitts fails to teach the use of an intermediate host. Applicants respectfully assert that Kitts fails to teach, suggest or provide motivation to derive applicants' invention as claimed.

Applicants respectfully assert that Patel fails to teach, suggest, or provide motivation to derive applicants' invention as claimed and fails to provide motivation to modify its teachings as suggested by the Examiner for the reasons provided in the previous section.

In view of the foregoing, applicants respectfully assert that one of ordinary skill in the art would not be motivated to combine the teachings of Kitts and Patel to derive applicants' invention as claimed with a reasonable expectation of success. Furthermore, modification of the teachings of Clark, as suggested by the Examiner, would fail to derive applicants' invention as claimed and would fail to result in a method possessing the advantages of applicants' invention. Applicants respectfully assert that Kitts, separately or in combination with Patel, fails to render applicants' invention obvious. Applicants request withdrawal of the rejection under 35 U.S.C. §103(a) over Clark in view of Patel.

Blissard in view of Patel

The Examiner maintains the rejection of Claims 27-34 and 43-50 under 35 U.S.C. §103(a) as obvious over Blissard *et al.* (hereinafter "Blissard") in view of Patel. Applicants cancelled Claims 43-50, thereby rendering their rejection moot. Applicants respectfully traverse the rejection of Claims 27-34.

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of Blissard with the teachings of Patel to achieve economy of time and reduce costs, and that the modification would result in applicants' invention, as claimed, with a reasonable expectation of success. Applicants disagree.

Blissard teaches using replication-defective whole virus particles lacking the GP64 gene to infect the cells at a different time than the rescue vector. The Blissard method results in a heterogeneous virus population, with a high proportion of viruses lacking the foreign gene insert, and a high degree of parental virus contamination. In contrast, in applicants' claimed method, the naked baculovirus DNA is used. The use of the naked DNA allows the transfection of cells with the baculovirus vector and the foreign DNA simultaneously, resulting in a homogenous virus population upon recombination.

The method taught in Patel uses yeast cells instead of insect cells to produce recombinant viruses. In contrast, applicants' invention, as claimed, does not use yeast cells to generate the recombinant baculovirus, but simply uses yeast cells to maintain the baculovirus vector. Patel fails to teach, suggest, or provide motivation to use insect cells to generate the recombinant virus in the insect systems. In fact, Patel teaches away from using insect systems for recombinant virus generation, asserting that it is the yeast system that allows the rapid generation of recombinant virus without any background parental virus.

Furthermore, combining the teachings of Patel with the teachings of Blissard would not result in an operable baculovirus system, because the whole viral particles

taught in Blissard are likely unsuitable for replication in a host other than the insect cells even if modified with an appropriate origin of replication. Viruses rely at least in part on the hosts' cellular machinery for transcription and translation. Viral host-specificity is well known.

In view of the foregoing, applicants respectfully assert that Blissard and Patel, alone or in combination, fail to teach, suggest, or provide motivation to derive all the elements of the applicants' invention, as claimed, and fail to render applicants' invention obvious. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over Blissard in view of Patel.

Applicants respectfully submit that this is a complete response to the Final Office Action dated April 20, 2004. Applicants respectfully assert that the claims are now in condition for allowance and request that the application be passed to issuance. If the Examiner believes that any informalities that may be corrected by Examiner's amendment remain in the case, or if there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

Elena S. Polovnikova, Ph.D.
Patent Agent
Reg. No. 52,130

KILPATRICK STOCKTON LLP
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309-4530
Phone: (404) 815-6500
Fax: (404) 815-6555
Attorney Docket: 46309-257438